Remarks

Claims 1-4, 13-14, 19-22, 31-32, 37-38, and 41-42 were pending in this application. Claims 2 and 20 are canceled herein. Claims 1, 3-4, 19-22 and 41 are amended herein. Support for the amendment of claims 1, 3-4 and 41 can be found throughout the specification, for example at page 30, lines 24-30. Claims 19-22 are amended to incorporate a limitation of original claim 20.

No new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1, 3-4, 13-14, 19, 21-22, 31-32, 37-38, and 41-42 are pending in this application.** Consideration of the pending claims is requested.

Telephone Conferences

Applicants thank Examiner VanderVegt for the helpful telephone conferences of January 26, 2006 wherein the Declaration of Ralph A. Tripp Under 37 C.F.R. § 1.132 was discussed. The amendment of the claims to be directed to inflammation of the lung, and the support for this amendment, was also discussed. Applicants also thank the Examiner for the brief telephone conference of March 14, 2006, wherein the data presented in the accompanying Declaration of Dr. Tripp was discussed.

Applicants believe that this amendment and the accompanying Declaration of Dr. Tripp address all of the outstanding rejections. If any matters remain to be addressed prior to the issuance of a Notice of Allowance, Applicants respectfully request an additional telephone conference with their undersigned representative.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-3, 13-14, 19-21, 31-32, 37-38, and 41-42 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kudlacz et al., in view of Jafarian et al., Hemmingsson et al., Moneret-Vautrin et al., and U.S. Patent No. 5,256,766 (herein after the "766 patent). Claims 2 and 20 are canceled herein, rendering this rejection moot as applied to these claims. Applicants respectfully disagree with the rejection as applied to claims 1, 3, 13-14, 19-21, 31-32, 27-38 and 41-42.

Kudlacz *et al.* discloses that substance P release occurs during periods of respiratory viral

infection which are temporarily correlated with airway hyper-responsiveness, and that in conditions associated with tissue inflammation substance P levels are increased in associated fluids. Kudlacz *et al.* does not teach the administration of anti-substance P antibodies to a subject, let alone the intranasal administration of anti-substance P antibody fragments to prevent/treat viral or bacterial-induced inflammation, or their use to reduce the levels of intracellular cytokines in a subject.

Jafarian *et al.* discloses that administration of a monoclonal anti-substance P antibody in guinea pigs can prevent the bronchospastic effects of exogenous substance P in these animals. Jafarian *et al.* does not teach the administration of anti-substance P **antibody fragments** to prevent/treat viral or bacterial-induced **inflammation,** or their use to reduce the levels of intracellular cytokines in a subject, let alone the intranasal administration of these antibodies.

Hemmingson et al. (Scand. J. Infect. Dis. 25(6): 783-985, 1993) describes that the nasal administration of non-specific immunoglobulins, mainly IgA, could be used for short-term physiological prophylaxis for the prevention of upper respiratory tract infections (colds) in healthy skiers. Hemmingson et al. does not suggest a role for substance P in upper respiratory tract infections, let alone the use of anti-substance P antibodies to treat inflammation of the lung.

Moneret-Vautrin et al. discloses that non-allergic rhinitis with eosinphilla syndrome (NARES), a syndrome of nasal hyperreactivity, is associated with an eosinophilic infiltrate. As NARES might be due to neurogenic inflammation, Moneret-Vautrin et al. suggest that "it would seem necessary to study the immunoreactivity of the NARES nasal mucosa for neuropeptides in general, and substance P in particular" (see page 167). Moneret-Vautrin et al. do not describe inflammatory conditions of the lung, let alone the administration of anti-substance P antibodies to treat inflammatory conditions of the lung.

The '766 patent discloses that the use of fragments (such as Fab and $F(ab')_2$) of antibodies that specifically bind **the thrombin receptor** can be used in a therapeutic context because these fragments are "generally less immunogenic" than the whole antibody. The '766 patent discloses that thrombin receptor antagonists, such as antibodies, can be administered by injection, such as intravenous, subcutaneous, intramuscular or intraperitoneal injection. Transmucosal and transdermal applications are also disclosed (see column 15, lines 35-45). The '766 patent further discloses that thrombin receptor antagonists can be administered topically, such as in the form of salves, pastes and gels (column 15, lines 60-64). The '766 patent does not describe the use of antibodies to substance P.

The legal standard applicable to determinations of obviousness based on the prior art was

reiterated by the Court of Appeals for the Federal Circuit in *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988):

> The consistent criterion for the determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art [citations omitted]. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** [emphasis added].

Therefore, three elements must be established in order to make a *prima facie* case of obviousness. First, the prior art must suggest, or provide the incentive for, the combination of references and/or their modification. Second, the combination and/or modification as suggested or motivated by the art must yield the process or invention claimed. Third, the prior art must provide a reasonable expectation of success of the claimed process. At no point may the Applicants' disclosure be used to satisfy any of the three elements. If any of these elements is absent, the obviousness rejection is unsupported.

In the present case, Applicants submit that no case of obviousness has been established. Nothing in Kudlacz *et al.*, which teaches substance P release during viral infection, suggests or provides motivation (either explicitly or implicitly) for combination with Jafarian *et al.* (or a modification of its teachings), which teaches the use of anti-substance P antibodies to prevent/treat branchospastic effects of exogenous substance P and neurokinin A. Further, there is nothing in either of these references that suggest combination with the work of Hemmingsson et al, who describes the intranasal use of non-specific immunoglobulins (mostly IgA) to prevent colds in skiers, or with the '766 patent, which describes the use of F(Ab) fragments of the thrombin receptor, or Moneret-Vautrin et al., who describes that NARES, a syndrome of nasal hyperreactivity, is associated with an eosinophilic infiltrate, and suggests investigating if substance P plays a role in NARES. Thus, it is only the Applicants' disclosure (and impermissible hindsight reconstruction) that leads to the combination of references. A *prima facie* case of obviousness must include a finding that one of ordinary skill in the art, at the time the invention was made, would have reasonably expected the claimed invention to work. (See *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *In re Dow Chem.* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Submitted herewith is a Declaration of Dr. Tripp under 37 C.F.R. § 1.132, documenting that one of skill in the art

would have predicted that $F(ab)_2$ anti-substance P antibodies fragments would be more efficacious and have less unwanted side effects when administered systemically (such as by injection) for the treatment of a lung inflammatory disorder. Thus, it was an unexpected finding that intranasal administration of anti-substance P antibodies provided a superior effect for the treatment of an inflammatory disorder of the lung.

Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 4, 40 and 22 are were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kudlacz et al., in view of Jafarian et al., Hemmingsson et al., Moneret-Vautrin et al., and U.S. Patent No. 5,256,766 (herein after the "766 patent), further in view of Larsen.

Kudlacz et al., in view of Jafarian et al., Hemmingsson et al., Moneret-Vautrin et al., and U.S. Patent No. 5,256,766 are discussed above. Larsen discloses that "insults" to the bronchial airways, such as infection by respiratory syncytial virus, result in inflammation and heightened reactivity. Larsen does not teach the use of $F(ab')_2$ anti-substance P antibody fragments, let alone the intranasal administration of these fragments. Thus, Larsen et al. does not make up for the deficiencies of Kudlacz et al., Jafarian et al., Hemmingsson et al., Moneret-Vautrin et al., and the '766 patent.

As discussed above, a *prima facie* case of obviousness must include a finding that one of ordinary skill in the art, at the time the invention was made, would have reasonably expected the claimed invention to work (see *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *In re Dow Chem.* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The Declaration of Dr. Tripp under 37 C.F.R. § 1.132 documents that one of skill in the art would have predicted that $F(ab)_2$ anti-substance P antibodies fragments would be more efficacious and have less unwanted side effects when administered systemically (such as by injection) for the treatment of a lung inflammatory disorder. Thus, it was an unexpected finding that intranasal administration of anti-substance P antibodies provided a superior effect for the treatment of an inflammatory disorder of the lung.

Reconsideration and withdrawal of the rejection is respectfully requested.

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Conclusion

It is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned agent prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application will expedite prosecution.

Respectfully submitted,

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